



## INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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| <b>(54) Title:</b> PHOSPHOCHOLINE LINKED PRODRUG DERIVATIVES   |           |   |
| <div style="text-align: center;"> <p style="text-align: right;">(I)</p> </div>   |           |   |
| <b>(57) Abstract</b><br><p>Disclosed are compounds of general formula (I) that function as prodrugs, thereby increasing bioavailabilities of the linked therapeutic agents, wherein the LINKER is (i) substituted or unsubstituted alkyl, (ii) substituted or unsubstituted alkenyl, (iii) substituted or unsubstituted alkanoyl, (iv) substituted or unsubstituted alkenoyl wherein the double bond is <i>cis</i>, and (v) (<i>ortho</i> or <i>para</i>) carbonyl-substituted aryl; and wherein the substituent is each an independent group or linked together thereby forming a ring; and wherein X is one or more substituted or unsubstituted group containing one or more O, N, or S atom and wherein the substituent is each an independent group or linked together thereby forming a ring; and wherein the therapeutic agent is an alcohol-containing water-insoluble steroids or another alcohol containing compounds and methods to prepare such compounds.</p> |           |   |

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## PHOSPHOCHOLINE LINKED PRODRUG DERIVATIVES

### FIELD OF THE INVENTION

The present invention is directed to a novel class of phosphocholine-linked derivatives which not only increase water solubility, but also function as true prodrugs, allow phosphocholines or phosphocholine congeners to be attached to a variety of functional groups on the therapeutic agent, and have the potential on being able to control the rate of release of the pharmaceutical agent.

### BACKGROUND OF THE INVENTION

Conventional means for delivering pharmaceutical and therapeutic agents to mammals often are severely limited by chemical and physical properties of the agent, such as aqueous solubility. For example, oral delivery of many biologically-active agents would be the route of choice if not for poor bioavailability due to the limited dissolution of the active agent and subsequent absorption.

Water insoluble therapeutic agents are particularly difficult to administer parenterally. Formulations often require inclusion of a variety of emulsifiers, such as CREMOPHOR® EL. But CREMOPHOR®, which is poly(oxyethylene)-40-castor oil, can result in hypotension, dyspnea, angioedema, or generalized urticaria. These hypersensitive reactions can lead to life-threatening conditions, and it is recommended that all patients be premedicated with corticosteroids, diphenhydramine, and H2 antagonists to avoid severe hypersensitivity.

Another emulsifier is administered in Propofol, an anesthetic. This emulsion contains soy bean oil, glycerol, and egg phosphatide that create a microbial contamination problem with the current formulation of propofol, which can result in life-threatening illness or death from fever, infection or sepsis. This is especially problematic for post-operative or intensive care unit (ICU) patients. Although U.S. Patent 5,714,120 discloses a method to minimize microbial contamination by the addition of a preservative, this formulation is not an antimicrobial preserved product by USP standards and extrinsic contamination remains problematic.

There is thus a need in the art for methods and compositions to enable potential therapeutic agents to be rendered soluble thereby circumventing the need for emulsifiers and providing for safer and more efficacious therapeutic agents.

#### SUMMARY OF THE INVENTION:

In one aspect, the present invention provides a method for enabling potential therapeutic agents to be rendered soluble comprising the steps of inserting one or more linker moieties having one or more primary alcohol group between a phosphocholine or a phosphocholine congener to the therapeutic agents having one or more compatible group.

In another aspect, the present invention provides a method for increasing the bioavailability of a pharmaceutical agent, comprising the steps of derivatizing the agent with one or more linker moieties, producing an intermediate, recovering and coupling the intermediate with phosphocholine or a phosphocholine-congener to the linkers, producing a final derivative and administering the final derivative to a mammal, wherein the agent in derivative form is significantly more soluble in aqueous media than the agent in non-derivatized form.

In yet another aspect, the present invention provides a composition of matter comprising an isolated phosphocholine linked via a linker to propofol, a sedative or anesthetic agent.

5 In yet another aspect, the present invention provides a pharmaceutical formulation for treating a mammal suffering from cancer comprising an isolated phosphocholine linked via a linker to paclitaxel and a physiologically acceptable vehicle, carrier, binder, preservative, stabilizer, flavor, etc., as called for by accepted pharmaceutical practice.

10 The aqueous solubilities of the compounds described herein are evaluated by several methods known in the art, such as preparing a saturated solution of the compound in water, removing a known volume of the solution, and quantitating the amount of the compound in that solution using standard  
15 analytical techniques, like HPLC or LC-MS.

These and other aspects of the present invention will be apparent to those of ordinary skill in the art in light of the present description, claims and drawings.

#### DETAILED DESCRIPTION OF THE INVENTION

20 The invention in its broad aspects relates to phosphocholine or phosphocholine congeners, attached via a linker, to a therapeutic agent.

25 Phosphocholine derivatives of therapeutic agents containing a primary alcohol or a phenol are readily cleaved by *phosphatases* and mammalian *esterases*. The preparation of phosphocholine derivatives of biologically active agents has been reported (e.g., U.S. Patent No. 5,703,063). However, if the phosphocholine is attached to a secondary or sterically hindered alcohol, hydrolysis or removal of the phosphocholine does not  
30 occur rapidly or to a large extent.

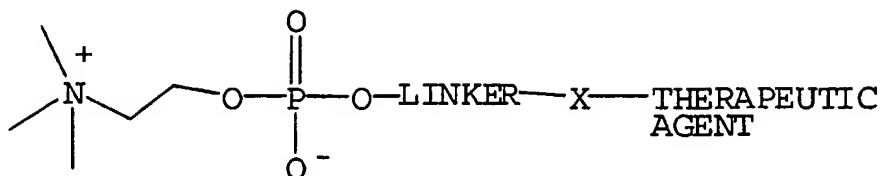
The present invention advantageously provides insertion of a linker between the phosphocholine and the secondary alcohol of the therapeutic agent wherein the phosphocholine is bound to the linker via a primary alcohol or phenol functional group inherent in the linker. This formulation facilitates enzymatic cleavage of the phosphocholine linker bond and liberates the primary alcohol or phenol of the linker. The linker then spontaneously eliminates to liberate the therapeutic agent and an inert molecule arising from the decomposed linker.

Poor water solubility of biologically active agents is, in many cases, the reason for poor bioavailability of the compounds. The compounds described herein display no less than 5 to 10-fold increased biological activity and/or aqueous solubility as compared to the non-derivatized therapeutic agents when administered by the same route. Preferably, the compounds display increased biological activity and/or aqueous solubility in the range from one hundred fold to one hundred thousand fold relative to the non-derivatized therapeutic agents. Thus, the compounds described herein are useful for the enhanced bioavailability of otherwise water-insoluble compounds.

The phosphocholine congeners include, but are not limited to, O-phosphoserine; O-phosphothreonine; O-phosphotyrosine and their mono- and di-N-methyl derivatives; O-phosphoethanolamine and their mono- and di-N-methyl derivatives.

Although the compounds of this invention can include phosphocholine or phosphocholine congeners, they will be described below as compounds having phosphocholine of general

FORMULA I:



wherein the LINKER is one or more of the groups selected from the group consisting of (i) substituted or unsubstituted alkyl, (ii) substituted or unsubstituted alkenyl, (iii) substituted or unsubstituted alkanoyl, (iv) substituted or unsubstituted alkenoyl wherein the double bond is *cis*, and (v) (*ortho* or *para*) carbonyl-substituted aryl; and

wherein the substituent is each an independent group or linked together thereby forming a ring; and

wherein X is one or more substituted or unsubstituted group containing one or more O, N, or S atom and

wherein the substituent is each an independent group or linked together thereby forming a ring; and

wherein the therapeutic agent is selected from the group consisting of alcohol-containing water-insoluble steroids and another alcohol containing compounds.

The (*ortho* or *para*) carbonyl-substituted aryl of the LINKER is selected from the group consisting of *ortho*-CR<sub>1</sub>R<sub>2</sub>-substituted aryl-CO, substituted aryl-*ortho*-CR<sub>3</sub>R<sub>4</sub>-CO, substituted aryl-*ortho*-CR<sub>3</sub>R<sub>4</sub>-CR<sub>5</sub>R<sub>6</sub>-CO, substituted aryl-*ortho*-CR<sub>3</sub>=CR<sub>4</sub>-CO wherein the double bond is *cis*, *ortho*-CR<sub>1</sub>R<sub>2</sub>-substituted aryl-CR<sub>5</sub>R<sub>6</sub>-CO, and substituted aryl-(*ortho* or *para*)-CO.

The aryl substituents may optionally be selected to accelerate or decelerate the rate of enzymatic cleavage of a phenolic phosphocholine. Examples of substituents accelerating the rate of enzymatic cleavage would be nitro, alkyl or aryl sulfonyl, alkyl or aryl keto, alkyl or aryl oxycarbonyl in the

ortho and/or para positions relative to the phenolic phosphocholine. Examples of substituents decelerating the rate of enzymatic cleavage of a phenolic phosphocholine would be alkyl, alkoxy, alkylthio in the ortho and/or para positions relative to the phenolic phosphocholine.

The aryl is selected from the group consisting of benzene, naphthalene, pyridine, pyrrole, thiophene, furan, imidazole, thiazole, oxazole, pyrimidine, indole, benzimidazole, benzthiazole, benzofuran, benzothiophene and quinoline, each bearing one or more of the group consisting of hydrogen, C<sub>1-8</sub>-alkyl, C<sub>1-8</sub>-alkoxy, F, Cl, Br, C<sub>1-8</sub>-alkoxycarbonyl, amino, substituted amino, nitro, C<sub>1-8</sub>-alkylthio, C<sub>1-8</sub>-alkyl sulfoxido, and C<sub>1-8</sub>-alkylsulfono.

In one embodiment, the present invention is a compound having a general formula I wherein (i) said alkyl has the formula CR<sub>1</sub>R<sub>2</sub>, (ii) said alkenyl has the formula CR<sub>1</sub>=CR<sub>3</sub>-CR<sub>4</sub>, (iii) said alkanoyl has the formula CR<sub>1</sub>R<sub>2</sub>-CR<sub>3</sub>R<sub>4</sub>-CR<sub>5</sub>R<sub>6</sub>-CO, (iv) said alkenoyl has the formula CR<sub>1</sub>R<sub>2</sub>-CR<sub>3</sub>=CR<sub>4</sub>-CO and wherein the double bond is *cis*, and (v) said substituted aryl has the formula aryl-CR<sub>1</sub>R<sub>2</sub>; and

wherein R<sub>1</sub>, R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub>, and R<sub>6</sub> are the same or different and are selected from the group consisting of

(i) hydrogen;  
(ii) linear, branched, and unsaturated C<sub>1-12</sub>-alkyl;  
(iii) substituted C<sub>1-8</sub>-alkyl, wherein the substituent is selected from the group consisting of Y1-Y24, wherein

Y1 is hydroxy,  
Y2 is C<sub>1-8</sub>-alkoxy,  
Y3 is carbo-C<sub>1-8</sub>-alkoxy,  
Y4 is C<sub>1-8</sub>-alkylamino,  
Y5 is di-C<sub>1-8</sub>-alkylamino,  
Y6 is C<sub>6-12</sub>-arylamino,  
Y7 is C<sub>6-12</sub>-aryloxy,  
Y8 is amino,



Y9 is amino-C<sub>2</sub>-C<sub>8</sub>-alkoxy,

Y10 is C<sub>1-8</sub>-alkylthio,

Y11 is C<sub>6-12</sub>-arylthio,

Y12 is acetamido,

5 Y13 is mercapto,

Y14 is benzamido,

Y15 is carboxamido,

Y16 is phthalimido,

Y17 is guanidino,

10 Y18 is ureido,

Y19 is isothioureido,

Y20 is carboxy,

Y21 is (C<sub>6-12</sub>)aryl-(C<sub>1-8</sub>)alkyl,

Y22 is (C<sub>6-12</sub>)aryl-(C<sub>2-8</sub>)alkenyl,

15 Y23 is aromatic heterocyclo(C<sub>1-8</sub>)alkyl,

and Y24 is aromatic heterocyclo-(C<sub>2-8</sub>)-alkenyl wherein the heterocyclic group of Y23 and Y24 have 5-10 ring atoms and have up to two O, N, or S heteroatoms; and(iv) substituted Y21 or substituted Y23 wherein the substituent is selected from the group consisting of Y1, Y2, Y4, Y5, Y7, Y8, Y12, Y14, Y17-Y20, and Y25-Y29 wherein

Y25 is halogen,

Y26 is C<sub>1-8</sub>-alkyl,

Y27 is amino-C<sub>1-8</sub>-alkyl,

25 Y28 is C<sub>6-12</sub>-aroyl, and

Y29 is C<sub>1-8</sub>-alkanoyl.

Unless specified otherwise: (i) alkyl, alkenyl and alkynyl denote straight and branched hydrocarbon chains having single, double and triple bonds, respectively; (ii) C<sub>6-12</sub>-aryl groups denote unsubstituted aromatic ring or rings such as, for example, phenyl or naphthyl; (iii) hetero denotes the heteroatoms O, N, or S; (iv) aromatic heterocyclic have five to ten ring atoms and contain up to four heteroatoms; (v) halogen or halo denote F, Cl, Br, or I atoms; and (vi) alkoxy denotes an alkyl group attached to O.

35

Examples of C<sub>1-8</sub>-alkyl or C<sub>2-8</sub> alkenyl groups include methyl, ethyl, propyl, isopropyl, butyl, t-butyl, sec-butyl, pentyl, isopentyl, hexyl, vinyl, allyl, butenyl and the like; aromatic heterocyclic group is selected from the group  
5 consisting of pyridyl, thienyl, furyl, indoyl, benzthienyl, imidazolyl, thiazolyl, quinolyl and isoquinoyl.

The compounds containing the R-groups described herein can be purchased from numerous commercial sources such as Sigma Chemical Company (St. Louis, MO), Aldrich Chemical Company  
10 (Milwaukee, WI), Acros Organic Chemicals (Pittsburgh, PA), or Fluka Chemical Corporation (Milwaukee, WI). All other compounds not directly available from commercial sources can be prepared from commercially available starting materials by anyone skilled in the art of synthetic organic chemistry.

15 The preferred linkers are the compounds wherein R<sub>1</sub> is hydrogen, and R<sub>2</sub>, R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> are the same or different and are selected from the group as defined above.

The most preferred linkers are compounds of the above formula wherein R<sub>1</sub> and R<sub>2</sub> are hydrogen and R<sub>3</sub>, R<sub>4</sub>, R<sub>5</sub> and R<sub>6</sub> are  
20 the same or different and are selected from the group as defined above.

More than one linker per therapeutic agent molecule can be present when more than one appropriate functional group (X) exists. In such case, the order of removal of multiple  
25 phosphocholines on a single therapeutic agent would depend on a number of factors: (i) steric effects, (ii) nature of linker, (iii) nature of X. Steric effects influencing the order of removal of multiple phosphocholines would be determined by the immediate steric environment of the specific  
30 phosphocholine-linked therapeutic agent. Sterically crowded phosphocholine-linked therapeutic agents would be predicted to be enzymatically cleaved more slowly than non-sterically crowded phosphocholine-linked therapeutic agents. Substituents on the linker may drive the elimination of the  
35 linker by sterically favoring a geometric form of the

intermediate linker-therapeutic agent which self-eliminates more rapidly. Variables in the nature of the linker include inherent differences in the kinetics of the decomposition of the various linkers, and include the nature of substituents of substituted phenyl based linker as described (above/below). Variables in the nature of X include electronic effects of X as a leaving group. Generally, the more electronically deficient X is a better leaving group and hence is eliminated more rapidly and regenerates the therapeutic agent faster than an electronically rich X.

X is selected the group containing one or more O, N, or S atom selected from the group consisting of O, (O)CO, NR<sub>8</sub>, NR<sub>8</sub> CO, NR<sub>8</sub> CO NR<sub>9</sub>, NR<sub>8</sub>(SO<sub>2</sub>), NR<sub>8</sub> CS, NR<sub>8</sub> CS NR<sub>9</sub>, ONR<sub>8</sub>, ONR<sub>8</sub>CO, NR<sub>8</sub>(O), NR<sub>8</sub>(O)CO, nitrogen heterocycles, amide and urea internal in the therapeutic agent.

R<sub>8</sub> and R<sub>9</sub> are the same or different and are selected from the group consisting of

- (i) hydrogen;
- (ii) linear, branched, and unsaturated C<sub>1-12</sub>-alkyl;
- (iii) substituted C<sub>1-8</sub>-alkyl, wherein the substituent is selected from the group consisting of Y1-Y13 and Y15-Y25;
- (iv) substituted Y21 or substituted Y23 wherein the substituent is selected from the group consisting of Y1, Y2, Y4, Y5, Y7, Y8, Y12, Y14, Y17-Y20, and Y25-Y29.

There may be more than one X in the therapeutic agent and, hence, more than one phosphocholine linked to the therapeutic agent.

R<sub>8</sub> and R<sub>9</sub> may be linked together thereby forming

- (i) a ring of three to six carbon atoms, or
- (ii) a ring of two to five carbon atoms and one O, or S heteroatom, or substituted heteroatom NR<sub>7</sub>; wherein R<sub>7</sub> is selected from the group consisting of Y21, Y26, and Y28-Y31.

R<sub>8</sub> and / or R<sub>9</sub> may be connected to the therapeutic agent molecule thereby forming alkylene bridge of from one to five carbon atoms and one or two O, S or NR<sub>7</sub> heteroatoms; wherein R<sub>7</sub> is selected from the group consisting of Y21, Y26,

Y28-Y31, and the pharmaceutically acceptable salts thereof.

Examples of therapeutic agents which benefit from a phosphocholine linker:

5 Numerous biologically active compounds suffer from low water solubility and poor bioavailability. One family of such compounds are steroids, which are in general, poorly bioavailable. The steroids include testosterone, cardiotonic steroids, and other steroids with biological activity.

10 Testosterone is prescribed therapeutically for men with low levels of endogenous testosterone. Delivery is problematic, however, and necessitates the use of, for example, a testosterone impregnated patch which must be applied directly to the shaven scrotum. A water soluble phosphocholine-linked prodrugs of testosterone could therefore  
15 be useful in circumventing delivery of the therapeutic agent.

Cardiotonic steroids, such as digitoxigenin, digoxigenin and ouabagenin are currently used therapeutically. However, their low levels of oral availability makes dosing difficult and the potential for an overdose an important  
20 consideration for the attending physician. Phosphocholine linked steroids have the potential to be delivered intravenously, nasally, perorally, intratracheally, administered by patch, etc.

25 Other steroids with biological activity are candidates for derivatization with phosphocholine linkers. Dehydroepiandrosterone (DHEA), etiocholanolone, pregnenolone, estradiol, estrone, dexamethasone and hydrocortisone are a few examples of steroids which could benefit by deriavatization with a phosphocholine linker.

30 Anti-neoplastic agents, for example, paclitaxel and other taxanes, etoposide, vincristine, vinblastine, and topoisomerase I inhibitors like camptothecin, irinotecan (Pharmacia & Upjohn, Kalamazoo, MI), topotecan (SmithKline Beecham, Philadelphia, PA), CPT11 (Bristol-Myers Squibb,  
35 Princeton, NJ); antiviral agents, including nucleoside analogs

and protease inhibitors, such as nelfinavir (Agouron, LaJolla, CA), saquinavir (Roche, Nutley, NJ), crixivan (Merck, West Point, PA), ritonavir (Abbott, N. Chicago, IL); antibiotics, particularly mitomycin, bleomycin, daunorubicin, doxorubicin, actinomycin, and amphotericin; anesthetics, such as propofol and barbituates, for use in general anesthesia or sedation; analgesics, such as morphine, codeine, and Ziconotide (Neurex, Menlo Park, CA); therapeutic peptides or peptidomimetics, composed of D-amino acids, L-amino acids, or amino acid analogs, acting as enzyme inhibitors, receptor ligands, or disruptors of protein-protein interactions, such as cyclosporin A; therapeutic polypeptides or proteins, such as leptin, growth hormone, calcitonin, vasopressin, renin, prolactin, thyroid and parathyroid hormones, corticotropin, corticotropin-releasing factor, follicle stimulating hormone, luteinizing hormone, gonadotropin, atrial peptides, isolated from natural sources or produced by recombinant DNA technology; nucleic acids, such as anti-sense oligonucleotides or nucleic acids for gene therapy, composed of ribo- or deoxyribonucleotides or nucleotide analogs. Unless otherwise noted, the compounds described herein can be purchased from numerous commercial sources, such as Sigma Chemical Company (St. Louis, MO, Calbiochem-Novabiochem (San Diego, CA), Research Biochemicals Inc. (Natick, MA), or Alexis Corp. (San Diego, CA).

Particularly preferred therapeutic agents for use in the present invention are Propofol and related anesthetic/sedative compounds. These compounds can be conjugated to phosphocholine or phosphocholine congeners via one or more linker pursuant to the present invention and used as anesthetic compounds. It is expected that these derivatized agents will be more effective due to their increased aqueous solubility.

Compounds of Formula I in pharmaceutical compositions

The derivatized prodrugs of the present invention can be incorporated into pharmaceutical formulations to be used to treat mammals. Pharmaceutical formulations comprising the phosphocholine linked prodrugs derivatives of the present invention as one or more of the active ingredients, would in addition optionally comprise pharmaceutically-acceptable carriers, diluents, fillers, salts and other materials well-known in the art depending upon the dosage form utilized. The compounds of this invention may be utilized in compositions such as tablets, capsules or elixirs for oral administration; suppositories for rectal administration; sterile solutions or suspensions for injectable administration; sterile solutions for ocular or internasal administration, and the like.

Animals in need of treatment using compounds of this invention can be administered dosages that will provide optimal efficacy. The dose and method of administration will vary from animal to animal and be dependent on such factors as weight, diet, concurrent medication and other factors which those skilled in the medical arts will recognize.

Typical formulation of compounds of Formula I as pharmaceutical compositions are discussed below. It will be appreciated that the unit content of active ingredient or ingredients contained in an individual dose or dosage form need not in itself constitute an effective amount for the various usages of the phosphocholine linked prodrugs derivatives of the present invention since the necessary effective amount can be reached by administration of a plurality of such dosage forms.

About 0.5 to 100 mg of a compound or mixture of compounds, as the zwitterionic phosphocholine or as a pharmaceutically acceptable salt, is compounded with a physiologically acceptable vehicle, carrier, binder, preservative, stabilizer, flavor, etc., as called for by accepted pharmaceutical practice. The amount of active

ingredients in these compositions is such that a suitable dosage in the range indicated is obtained.

Typical adjuvants which may be incorporated into tablets, capsules and the like are a binder such as acacia, corn starch or gelatin; an excipient such as microcrystalline cellulose; a disintegrating agent like corn starch or alginic acid; a lubricant such as magnesium stearate; a sweetening agent such as peppermint, wintergreen or cherry. When the dosage form is in a capsule, in addition to the above materials it may also contain a liquid carrier such as a fatty oil.

Other materials of various types may be used as coatings or as modifiers of the physical form of the dosage unit. A syrup or elixir may contain the active compound, a sweetener such as sucrose, preservatives such as propyl paraben, a coloring agent and a flavoring agent such as cherry. Sterile compositions for injection can be formulated according to conventional pharmaceutical practice. For example, dissolution or suspension of the active compound in a vehicle such as water or naturally occurring vegetable oil like sesame, peanut, or cottonseed oil or a synthetic fatty vehicle like ethyl oleate or the like may be desired.

Buffers, preservatives, antioxidants and the like can be incorporated according to the acceptable pharmaceutical practice.

The products of Formula I can be made by using the following general synthetic scheme. The definitions of the substituent groups are the same as for Formula I except where noted. The following examples of reagents are intended to further illustrate the present invention without limiting it thereof.

GENERAL SYNTHETIC SCHEME

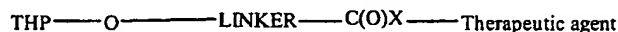


Where Therapeutic agent = alcohol containing water insoluble steroids or another alcohol containing compound as defined in the specification; and

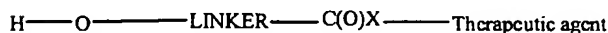
where X = O, N, or S containing groups as defined in the specification; and

where LINKER = unsubstituted or substituted alkyls or phenyls as defined in the specification; and where the primary alcohol part of the LINKER is protected with a tetrahydropyran (THP) or another alcohol protecting groups.

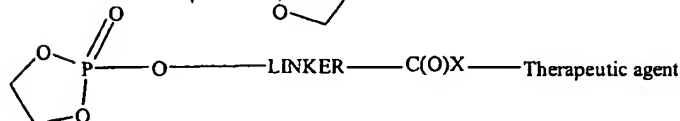
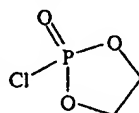
DCC  
DMAP  
CHCl<sub>3</sub>



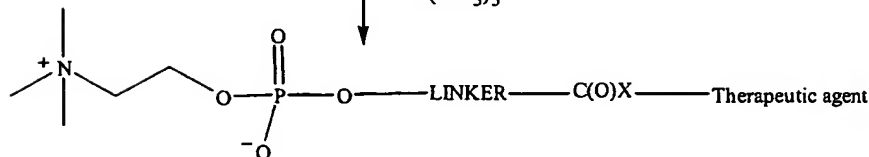
Dowex (H<sup>+</sup>)



N(CH<sub>2</sub>CH<sub>3</sub>)<sub>3</sub>



N(CH<sub>3</sub>)<sub>3</sub>

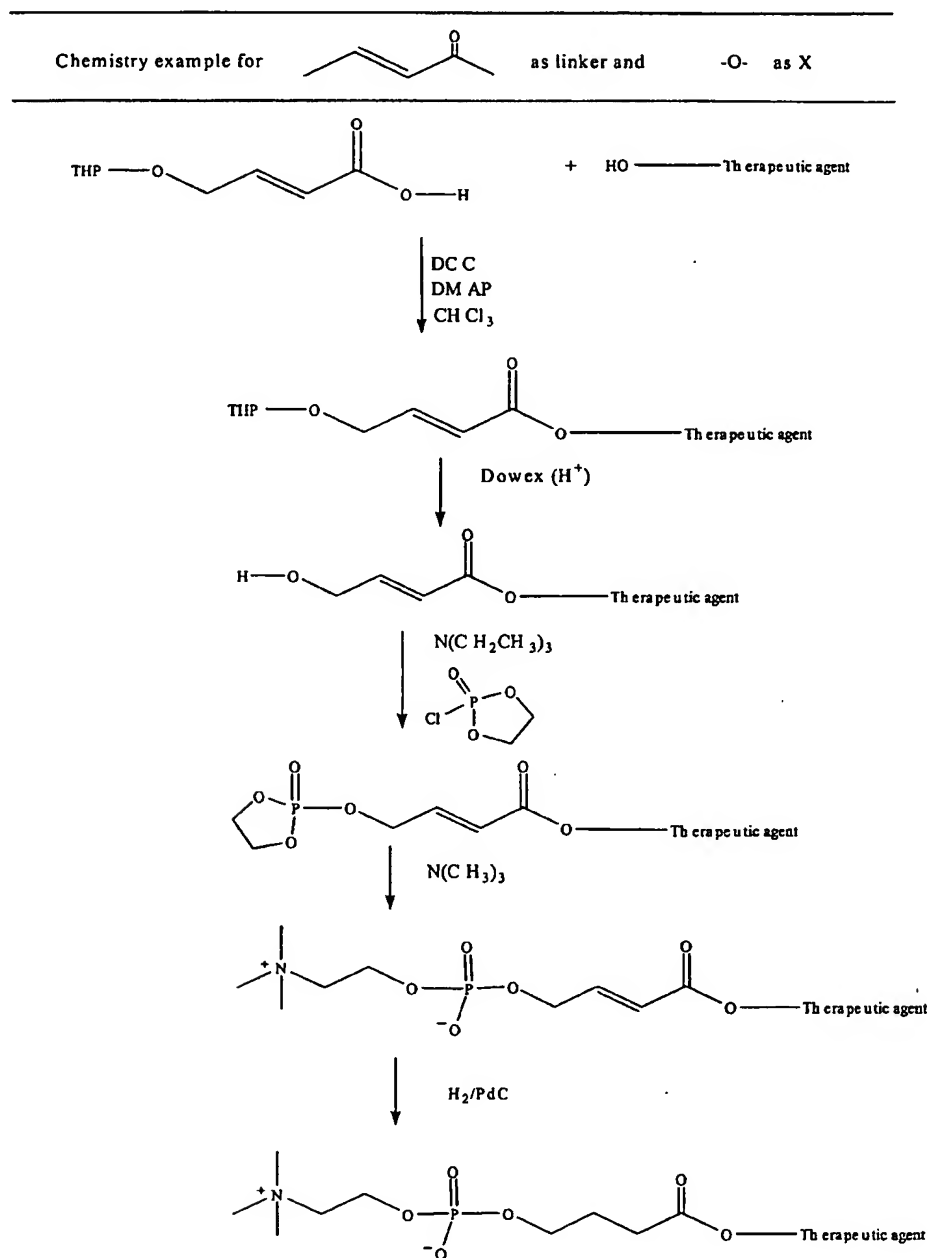


(FORMULA I)



The preferred products of Formula I can also be made by using the method depicted below. The definitions of the substituent groups are the same as for Formula I except where noted.

5



The following examples of compounds of Formula I by using Propofol as a therapeutic agent are illustrated in Example 1 below in Methods A or B. The biological activity of

10

phosphocholine linked prodrugs derivatives of the present invention are illustrated in the Example 2. Both examples are intended to further illustrate the present invention without limiting it thereof. The definitions of the substituent groups are the same as for Formula I except where noted.

### Example 1

#### Method A

Preparation of Phosphocholine-linked Propofol (sedative/anesthetic){2',6'-Diisopropylphenyl 4-(2-trimethyl ammonium ethyloxy)phosphonobutyrate}.

Ethyl 4-hydroxycrotonate (*trans*) (Kende, Org. Syn. Col. Vol. VII, p221) was treated with 2,3-dihydropyran and catalytic toluenesulfonic acid, according to Bernady (J. Org. Chem. 44, 1438, 1979) to yield ethyl 4-[2-tetrahydro  
pyranyl]oxycrotonate (*trans*). This compound was further treated with 0.1M LiOH in tetrahydrofuran, to yield the free acid (4-[2-tetrahydropyranyl] oxycrotonic acid), after acidification and work-up. This carboxylic acid was then coupled, via an ester bond, to 2,6-diisopropylphenol, utilizing *N,N*-dicyclohexyl-carbodiimide. After chromatographic purification on silica gel, the ester was then treated, in methanol, with a catalytic amount of Dowex 50W ion exchange resin to affect the removal of the tetrahydropyranyl protecting group. The resulting alcohol was treated with 2-chloro-2-oxo-1,3,2-dioxaphospholane in the presence of triethylamine in chloroform. Upon completion of this reaction, the isolated phosphate intermediate was dissolved in acetonitrile, charged with trimethylamine, and heated @ 80°C for 72 hours. After removal of trimethylamine, the solvent was removed in vacuo, the residue was partitioned between ethyl acetate and water. Freezing and lyophilization of the aqueous phase yielded the 4-O-phosphocholine. This compound was then hydrogenated in water to yield the title compound. LC/MS, NMR, and combustion data are available.

Method B

Preparation of Phosphocholine-linked Propofol (Sedative, anesthetic) {2',6'-Diisopropylphenyl 3-[ortho-(O-trimethylammoniummethyl phosphonooxy)]propionate}.

5 To a solution of 3g of 2-hydroxycinnamic acid (trans) in 60mL of dry chloroform was added 7.6mL (eq) of triethylamine. This solution was cooled in an ice bath and 5.7g (2.2eq) of 2-chloro-1,3,5-dioxaphospholane-2-oxide was added dropwise at 0°C. The reaction was allowed to stir at  
10 room temperature for thirty minutes. A solution of 2,6 diisopropylphenol (Propofol) in 20mL of chloroform was added and the reaction was stirred at room temperature for 16hr. The reaction was then washed three times with water, and then dried (MgSO<sub>4</sub>). Filtration and evaporation of the solvent  
15 yielded 10.5g of crude 2',6'-diisopropylphenyl 3-[ortho-(O-ethylene phosphonooxy)]propionate. This intermediate was treated with excess trimethylamine in acetonitrile in a pressure vessel at 80°C for 72hr. Removal of the excess trimethylamine and evaporation of the acetonitrile yielded the  
20 crude phosphocholine derivative of 2',6'- diisopropyl phenyl 2-hydroxycinnamate. This intermediate was purified by chromatography (silica gel, CHCl<sub>3</sub>/MeOH/H<sub>2</sub>O 40:55:5) yielding approximately 100mg of material. Hydrogenation of this intermediate in aqueous ethanol, employing 5%Pd/C yielded the  
25 title compound. LC/MS and NMR data are available.

Example 2Sleep indication in mice

The method which detects sedative activity following the protocol described by Simon et al. (*J. Pharmacol. Paris*,  
30 13:241-252, 1982).

Mice (10 per group) are placed in Plexiglass cages (20 x 10 x 10 cm) and administered the test substance, propofol, produced as above as an i.v. bolus in two seconds. The latency to sleep and the occurrence of sedation/sleep are  
35 noted over a period of one hour. Sleep is indicated by the

loss of the righting reflex. Animals within a group are tested sequentially and the test is performed blind. The test substance will be evaluated in 5 escalating doses. Unmodified propofol (16 mg per kg) administered in the same experimental conditions, will be used as a reference compound. The LD<sub>50</sub> for hypnotic activity is calculated following the method of Lichtfield and Wilcoxin (*J. Pharmacol. Exp. Ther.* 96:99-113, 1949).

Lethal dose 50 (LD<sub>50</sub>) in mice

The method, which determines the acute dose of a test substance causing 50% of death in a given animal species, follows the method described by Lichtfield and Wilcoxin.

After an 18 hour period of food deprivation but free access to water, mice will be administered the test substance as an i.v. bolus in two seconds. The appearance of morbidity, including local reaction and mortality, are noted for a period of 7 days, during which the animals have free access to food and water.

Ten mice are studied per group. The test is performed blind.

The test substance will be evaluated at 5 escalating doses.

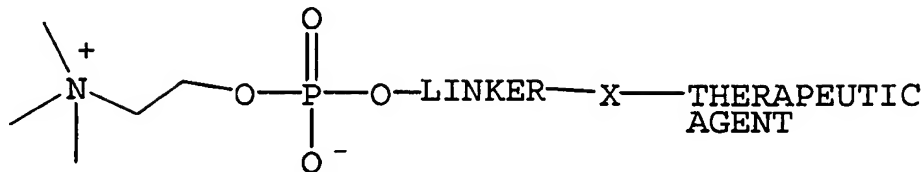
No reference substance and no control group are offered for this experiment.

The LD<sub>50</sub> is calculated at the end of the testing following the method of Lichtfield and Wilcoxin see *J. Pharmacol. Exp. Ther.* 96:99-113, 1949 above.

Variations of the present invention will suggest themselves to those skilled in the art, and are within the scope of the following claims:

We Claim:

1. A compound having the general formula I:



wherein the LINKER is one or more of the groups selected from the group consisting of (i) substituted or unsubstituted alkyl, (ii) substituted or unsubstituted alkenyl, (iii) substituted or unsubstituted alkanoyl, (iv) substituted or unsubstituted alkenoyl wherein the double bond is *cis*, and (v) (*ortho* or *para*) carbonyl-substituted aryl; and

wherein the substituent is each an independent group or linked together thereby forming a ring; and

wherein X is one or more substituted or unsubstituted group containing one or more O, N, or S atom and

wherein the substituent is each an independent group or linked together thereby forming a ring; and

wherein the therapeutic agent is selected from the group consisting of alcohol- containing water-insoluble steroids and another alcohol containing compounds.

2. A compound according to claim 1, wherein

(i) said alkyl has the formula  $\text{CR}_1\text{R}_2$ , (ii) said alkenyl has the formula  $\text{CR}_1=\text{CR}_3\text{---CR}_4$ , (iii) said alkanoyl has the formula  $\text{CR}_1\text{R}_2\text{---CR}_3\text{R}_4\text{---CR}_5\text{R}_6\text{---CO}$ , (iv) said alkenoyl has the formula  $\text{CR}_1\text{R}_2\text{---CR}_3=\text{CR}_4\text{---CO}$  and wherein the double bond is *cis*, and (v) said substituted aryl has the formula  $\text{aryl---CR}_1\text{R}_2$ ; and

wherein  $\text{R}_1$ ,  $\text{R}_2$ ,  $\text{R}_3$ ,  $\text{R}_4$ ,  $\text{R}_5$ , and  $\text{R}_6$  are the same or

8 different and are selected from the group consisting of  
9 (i) hydrogen;  
10 (ii) linear, branched, and unsaturated C<sub>1-12</sub>-alkyl;  
11 (iii) substituted C<sub>1-8</sub>-alkyl, wherein the substituent is  
12 selected from the group consisting of Y1-Y24, wherein  
13 Y1 is hydroxy,  
14 Y2 is C<sub>1-8</sub>-alkoxy,  
15 Y3 is carbo-C<sub>1-8</sub>-alkoxy,  
16 Y4 is C<sub>1-8</sub>-alkylamino,  
17 Y5 is di-C<sub>1-8</sub>-alkylamino,  
18 Y6 is C<sub>6-12</sub>-arylamino,  
19 Y7 is C<sub>6-12</sub>- aryloxy,  
20 Y8 is amino,  
21 Y9 is amino-C<sub>2</sub>-C<sub>8</sub>-alkoxy,  
22 Y10 is C<sub>1-8</sub>-alkylthio,  
23 Y11 is C<sub>6-12</sub>-arylthio,  
24 Y12 is acetamido,  
25 Y13 is mercapto,  
26 Y14 is benzamido,  
27 Y15 is carboxamido,  
28 Y16 is phthalimido,  
29 Y17 is guanidino,  
30 Y18 is ureido,  
31 Y19 is isothioureido,  
32 Y20 is carboxy,  
33 Y21 is (C<sub>6-12</sub>)aryl-(C<sub>1-8</sub>)alkyl,  
34 Y22 is (C<sub>6-12</sub>)aryl-(C<sub>2-8</sub>)alkenyl,  
35 Y23 is aromatic heterocyclo(C<sub>1-8</sub>)alkyl,  
36 and Y24 is aromatic heterocyclo(C<sub>2-8</sub>)alkenyl wherein  
37 the heterocyclic group of Y23 and Y24 have 5 - 10 ring atoms and  
38 comprises up to two O, N, or S heteroatoms; and  
39 (iv) substituted Y21 or substituted Y23 wherein the  
40 substituent is selected from the group consisting of  
41 Y1, Y2, Y4, Y5, Y7, Y8, Y12, Y14, Y17-Y20, and Y25-Y29 wherein

42 Y25 is halogen,  
43 Y26 is C<sub>1-8</sub>-alkyl,  
44 Y27 is amino-C<sub>1-8</sub>-alkyl,  
45 Y28 is C<sub>6-12</sub>-aroyl, and  
46 Y29 is C<sub>1-8</sub>-alkanoyl.

1 3. A compound according to claim 2, wherein said  
2 R<sub>1</sub> and R<sub>2</sub>; R<sub>1</sub> and R<sub>3</sub>; R<sub>2</sub> and R<sub>3</sub>; R<sub>3</sub> and R<sub>4</sub>; R<sub>3</sub> and R<sub>5</sub>; and R<sub>5</sub> and R<sub>6</sub>  
3 are linked together thereby forming:  
4 (i) a ring of three to six carbon atoms, or  
5 (ii) a ring of two to five carbon atoms and one O, or S  
6 heteroatom, or substituted heteroatom NR<sub>7</sub>; wherein R<sub>7</sub> is selected  
7 from the group consisting of Y21, Y26, Y28, Y29, and Y30-Y31,  
8 wherein Y30 is C<sub>3-8</sub>-alkenyl, and  
9 Y31 is C<sub>6-12</sub>-aryl.

1 4. A compound according to claim 2 wherein the group  
2 containing one or more O, N, or S atom is selected from the group  
3 consisting of O, (O)CO, NR<sub>8</sub>, NR<sub>8</sub>CO, NR<sub>8</sub>CO NR<sub>9</sub>, NR<sub>8</sub>(SO<sub>2</sub>), NR<sub>8</sub>CS,  
4 NR<sub>8</sub>CS NR<sub>9</sub>, ONR<sub>8</sub>, ONR<sub>8</sub>CO, NR<sub>8</sub>(O), NR<sub>8</sub>(O)CO, nitrogen heterocycles,  
5 amide and urea internal in therapeutic agent; and  
6 wherein R<sub>8</sub> and R<sub>9</sub> are the same or different and are  
7 selected from the group consisting of  
8 (i) hydrogen;  
9 (ii) linear, branched, and unsaturated C<sub>1-12</sub>-alkyl;  
10 (iii) substituted C<sub>1-8</sub>-alkyl, wherein the substituent is  
11 selected from the group consisting of Y1-Y13 and Y15-Y25;  
12 (iv) substituted Y21 or substituted Y23 wherein the  
13 substituent is selected from the group consisting of Y1, Y2, Y4,  
14 Y5, Y7, Y8, Y12, Y14, Y17-Y20, and Y25-Y29.

1 5. A compound according to claim 4 wherein R<sub>8</sub> and R<sub>9</sub>  
2 are linked together thereby forming  
3 (i) a ring of three to six carbon atoms, or

4 (ii) a ring of two to five carbon atoms and one O, or S  
5 heteroatom, or substituted heteroatom NR<sub>7</sub>; wherein R<sub>7</sub> is selected  
6 from the group consisting of Y21, Y26, and Y28-Y31.

1 6. A compound according to claim 4 wherein R<sub>8</sub>, R<sub>9</sub>, or  
2 both are connected to the therapeutic agent molecule thereby  
3 forming alkylene bridge of from one to five carbon atoms and  
4 one or two O, S or NR<sub>7</sub> heteroatoms; wherein R<sub>7</sub> is selected from  
5 the group consisting of Y21, Y26, Y28-Y31, and the  
6 pharmaceutically acceptable salts thereof.

1 7. A compound according to claim 5 wherein R<sub>8</sub>, R<sub>9</sub>, or  
2 both are connected to the therapeutic agent molecule thereby  
3 forming alkylene bridge of from one to five carbon atoms and  
4 one or two O, S or NR<sub>7</sub> heteroatoms; wherein R<sub>7</sub> is selected from  
5 the group consisting of Y21, Y26, Y28-Y31; and the  
6 pharmaceutically acceptable salts thereof.

1 8. A compound according to claim 2, wherein said  
2 (ortho or para) carbonyl-substituted aryl is selected from the  
3 group consisting of ortho-CR<sub>1</sub>R<sub>2</sub>-substituted aryl-CO, substituted  
4 aryl-ortho-CR<sub>3</sub>R<sub>4</sub>-CO, substituted aryl-ortho-CR<sub>3</sub>R<sub>4</sub>-CR<sub>5</sub>R<sub>6</sub>-CO,  
5 substituted aryl-ortho-CR<sub>3</sub>=CR<sub>4</sub>-CO wherein the double bond is cis,  
6 ortho-CR<sub>1</sub>R<sub>2</sub>-substituted aryl-CR<sub>5</sub>R<sub>6</sub>-CO, and substituted aryl-(ortho  
7 or para)-CO.

1 9. A compound according to claim 2, wherein said aryl  
2 is selected from the group consisting of benzene, naphthalene,  
3 pyridine, pyrrole, thiophene, furan, imidazole, thiazole,  
4 oxazole, pyrimidine, indole, benzimidazole, benzthiazole,  
5 benzofuran, benzothiophene and quinoline, each bearing one or  
6 more of the group consisting of hydrogen, C<sub>1-8</sub>-alkyl, C<sub>1-8</sub>-alkoxy,  
7 F, Cl, Br, C<sub>1-8</sub>-alkoxycarbonyl, amino, substituted amino, nitro,



8 C<sub>1-8</sub>-alkylthio, C<sub>1-8</sub>-alkylsulfoxido, and C<sub>1-8</sub>-alkylsulfono.

1 10. A compound according to claim 2, wherein R<sub>1</sub> is  
2 hydrogen.

1 11. A compound according to claim 2, wherein R<sub>1</sub> and  
2 R<sub>2</sub> are hydrogen.

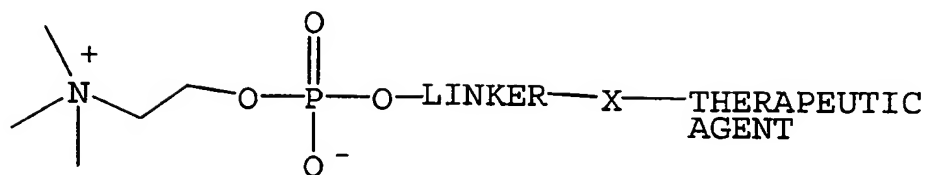
1 12. A compound according to claim 1, wherein the  
2 therapeutic agent is selected from the group consisting of  
3 Propofol and related anesthetic or sedative compounds.

1 13. A compound according to claim 1, wherein said  
2 water-insoluble steroids are selected from the group consisting  
3 of (i) testosterone, (ii) cardiotonic steroids selected from the  
4 group consisting of digitoxigenin, digoxigenin and  
5 ouabugenin, (iii) dehydroepiandrosterone (DHEA), (iv)  
6 etiocholanolone, (v) pregnenolone, (vi) estradiol, (vii) estrone,  
7 (viii) dexamethasone and (ix) hydrocortisone.

1 14. A compound according to claim 1, further comprises  
2 one or more of the ingredients selected from the group consisting  
3 of pharmaceutically-acceptable carriers, diluents, fillers,  
4 salts, buffers, preservatives, antioxidants, a binder, an  
5 excipient, a disintegrating agent, a lubricant, and a sweetening  
6 agent.

1 15. A compound according to claim 1 incorporated into  
2 tablets, capsules or elixirs for oral administration;  
3 suppositories for rectal administration; sterile solutions or  
4 suspensions for injectable administration; sterile solutions for  
5 ocular (?) or internasal administration.

16. A compound having the general formula I:

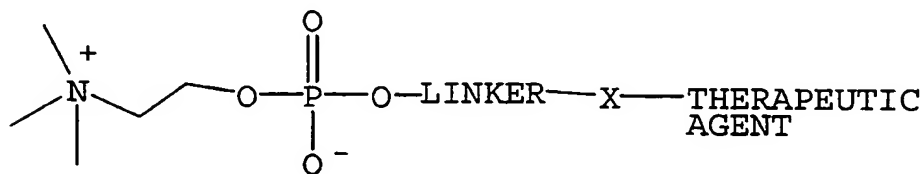


wherein the LINKER is a substituted alkenyl of formula  $\text{CR}_1\text{R}_2\text{---}\text{CR}_3\text{=CR}_4\text{---CO}$ , wherein  $\text{R}_1$ ,  $\text{R}_3$ , and  $\text{R}_4$  are hydrogen and wherein the double bond is *trans*, and

wherein X is O and

wherein the therapeutic agent is 2',6'-diisopropyl phenol.

17. A compound having the general formula I:



wherein the LINKER is a substituted alkanoyl of formula  $\text{CR}_1\text{R}_2\text{---}\text{CR}_3\text{R}_4\text{---}\text{CR}_5\text{R}_6\text{---CO}$ , wherein  $\text{R}_1, \text{R}_2, \text{R}_3, \text{R}_4, \text{R}_5$ , and  $\text{R}_6$  are H, and

wherein X is O and

1            wherein the therapeutic agent is 2',6'-diisopropyl  
2 phenol.

1            18. A method for enabling potential therapeutic agents  
2 to be rendered soluble comprising the steps of inserting one or  
3 more linker moieties having one or more primary alcohol group  
4 between a phosphocholine or a phosphocholine congener to the  
5 therapeutic agents having one or more alcohol group.

1            19. A method for increasing the bioavailability of  
2 pharmaceutical agent comprising the steps of derivatizing the  
3 agent with one or more linker moieties, producing an  
4 intermediate, recovering and coupling the intermediate with  
5 phosphocholine or a phosphocholine-congener to the linkers,  
6 producing a final derivative and administering the final  
7 derivative to a mammal, wherein the agent in derivative form is  
8 significantly more soluble in aqueous media than the agent in  
9 non-derivatized form.

1            20. The method of claim 19 wherein the pharmaceutical  
2 agent is propofol.

1            21. A pharmaceutical formulation for treating a mammal  
2 suffering from cancer comprising an isolated phosphocholine  
3 linked via a linker to paclitaxel and a physiologically  
4 acceptable vehicle, carrier, binder, preservative, stabilizer, or  
5 flavor as called for by accepted pharmaceutical practice.

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/04140

| <b>A. CLASSIFICATION OF SUBJECT MATTER</b><br>IPC(7) : A61K 9/127, 31/665, 31/675, 31/685; C07D 259/00, 487/22; C07F 9/02<br>US CL : 424/450; 514/77, 79, 80, 81, 82, 85, 86, 92, 99, 100; 540/456, 460, 478; 544/243, 337; 546/23; 548/113, 119; 549/220, 221, 222; 552/506, 507; 558/170, 171, 174  |  |   |  |  |   |  |  |      |   |  |      |   |   |  |  |  |  |  |  |  |
|---|--|---|--|--|---|--|--|------|---|--|------|---|---|--|--|--|--|--|--|--|
| <b>B. FIELDS SEARCHED</b><br>Minimum documentation searched (classification system followed by classification symbols)<br>U.S. : Please See Continuation Sheet<br><br>Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched<br><br>Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)<br>CAS ONLINE   |  |   |  |  |   |  |  |      |   |  |      |   |   |  |  |  |  |  |  |  |
| <b>C. DOCUMENTS CONSIDERED TO BE RELEVANT</b> <table border="1"> <thead> <tr> <th>Category *</th> <th>Citation of document, with indication, where appropriate, of the relevant passages</th> <th>Relevant to claim No.</th> </tr> </thead> <tbody> <tr> <td>A</td> <td>US 5,830,432 A (CHASALOW) 03 November 1998.</td> <td>1-21</td> </tr> <tr> <td>A</td> <td>WO 98/11906 A1 (AMUR PHARMACEUTICALS, INC.) 26 March 1998.</td> <td>1-21</td> </tr> </tbody> </table>  |  |   | Category *                               | Citation of document, with indication, where appropriate, of the relevant passages | Relevant to claim No.   | A  | US 5,830,432 A (CHASALOW) 03 November 1998.  | 1-21 | A   | WO 98/11906 A1 (AMUR PHARMACEUTICALS, INC.) 26 March 1998.   | 1-21 |   |   |  |  |  |  |  |  |  |
| Category *  | Citation of document, with indication, where appropriate, of the relevant passages   | Relevant to claim No.   |  |  |   |  |  |      |   |  |      |   |   |  |  |  |  |  |  |  |
| A   | US 5,830,432 A (CHASALOW) 03 November 1998.  | 1-21  |  |  |   |  |  |      |   |  |      |   |   |  |  |  |  |  |  |  |
| A   | WO 98/11906 A1 (AMUR PHARMACEUTICALS, INC.) 26 March 1998.   | 1-21  |  |  |   |  |  |      |   |  |      |   |   |  |  |  |  |  |  |  |
| <input type="checkbox"/> Further documents are listed in the continuation of Box C. <input type="checkbox"/> See patent family annex.   |  |   |  |  |   |  |  |      |   |  |      |   |   |  |  |  |  |  |  |  |
| <table border="0"> <tr> <td colspan="2">           * Special categories of cited documents:         </td> <td>           "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention         </td> </tr> <tr> <td>           "A" document defining the general state of the art which is not considered to be of particular relevance         </td> <td>           "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone         </td> <td></td> </tr> <tr> <td>           "E" earlier application or patent published on or after the international filing date         </td> <td>           "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art         </td> <td></td> </tr> <tr> <td>           "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)         </td> <td>           "A" document member of the same patent family         </td> <td></td> </tr> <tr> <td>           "O" document referring to an oral disclosure, use, exhibition or other means         </td> <td></td> <td></td> </tr> <tr> <td>           "P" document published prior to the international filing date but later than the priority date claimed         </td> <td></td> <td></td> </tr> </table> |  |   | * Special categories of cited documents: |  | "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention | "A" document defining the general state of the art which is not considered to be of particular relevance | "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone |      | "E" earlier application or patent published on or after the international filing date | "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |      | "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) | "A" document member of the same patent family |  | "O" document referring to an oral disclosure, use, exhibition or other means |  |  | "P" document published prior to the international filing date but later than the priority date claimed |  |  |
| * Special categories of cited documents:  |  | "T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention |  |  |   |  |  |      |   |  |      |   |   |  |  |  |  |  |  |  |
| "A" document defining the general state of the art which is not considered to be of particular relevance  | "X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone   |   |  |  |   |  |  |      |   |  |      |   |   |  |  |  |  |  |  |  |
| "E" earlier application or patent published on or after the international filing date   | "Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art |   |  |  |   |  |  |      |   |  |      |   |   |  |  |  |  |  |  |  |
| "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)   | "A" document member of the same patent family  |   |  |  |   |  |  |      |   |  |      |   |   |  |  |  |  |  |  |  |
| "O" document referring to an oral disclosure, use, exhibition or other means  |  |   |  |  |   |  |  |      |   |  |      |   |   |  |  |  |  |  |  |  |
| "P" document published prior to the international filing date but later than the priority date claimed  |  |   |  |  |   |  |  |      |   |  |      |   |   |  |  |  |  |  |  |  |
| Date of the actual completion of the international search<br>10 May 2000 (10.05.2000)   |  | Date of mailing of the international search report<br><b>09 JUN 2000</b>  |  |  |   |  |  |      |   |  |      |   |   |  |  |  |  |  |  |  |
| Name and mailing address of the ISA/US<br>Commissioner of Patents and Trademarks<br>Box PCT<br>Washington, D.C. 20231<br>Facsimile No. (703)305-3230  |  | Authorized officer<br><i>Mukund Shah</i><br>Telephone No. 703-308-1235  |  |  |   |  |  |      |   |  |      |   |   |  |  |  |  |  |  |  |

# INTERNATIONAL SEARCH REPORT

International application No.

PCT/US00/04140

**Continuation of B. FIELDS SEARCHED Item 1:** 424/450; 514/77, 79, 80, 81, 82, 85, 86, 92, 99, 100; 540/456, 460, 478; 544/243, 337; 546/23; 548/113, 119; 549/220, 221, 222; 552/506, 507; 558/170, 171, 174

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